

NCI Protocol #:05-C-0191H

**A Phase I Study of Image Guided Dose Escalation with Intensity Modulated
Radiation Therapy (IMRT)
to Histologically Confirmed Regions of Prostate Cancer**

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PRECIS

BACKGROUND

- This study represents a progression from findings in four previous NCI ROB protocols (02-C-0167A, 02-C-0207E, 03-C-0190B, 04-C-0171). In these previous works we have begun to develop techniques to obtain MR biological images and co-register tissue in prostate cancer patients.

OBJECTIVES

- The scientific objective of this protocol is to determine the maximum tolerated dose (MTD) of external beam radiation to regions of interest within the prostate based acute toxicity.
- Secondary objectives of this study are to relate patterns in gene and protein expression to response and toxicity and to evaluate the frequency of late term toxicity.

ELIGIBILITY

- Patients with prostate cancer without evidence of metastasis will be eligible for this study.

DESIGN

- This phase I trial will use intensity modulated radiation therapy (IMRT) to deliver escalating doses of external beam radiation to regions of histologically confirmed prostate cancer. The study will be conducted using a standard 3-6 dose-escalation with an initial 3 patients in each dose cohort and the potential expansion of the cohort to 6 patients.
- Anatomic MRI and MR biological images, such as MRS, will be obtained. Tissue will be acquired from sites of interest, with biopsy locations precisely translated (co-registered) to an MR image of reference. Tissue samples will be processed for cDNA microarray testing and stored for future analysis in the Radiation Oncology Branch, NCI. A gold seed will be left at the biopsy site as a fiducial marker to direct future radiation therapy. If necessary, additional fiducial markers will be placed for target localization during treatment.
- Once MR guided biopsies are obtained and fiducial markers placed, the patient will undergo a standard CT simulation for radiation therapy treatment planning. The MR and CT images will be fused. Areas of pathologically confirmed malignancy will undergo dose escalation as described above. Areas of image abnormality that could not be biopsied or were without definite pathologic evidence of malignancy will be given intermediate doses. The remainder of the prostate gland will receive standard dose (7560 cGy.) [1, 2]
- The trial will accrue 18 to 36 patients with an anticipated accrual period of 2 years.

SCHEMA

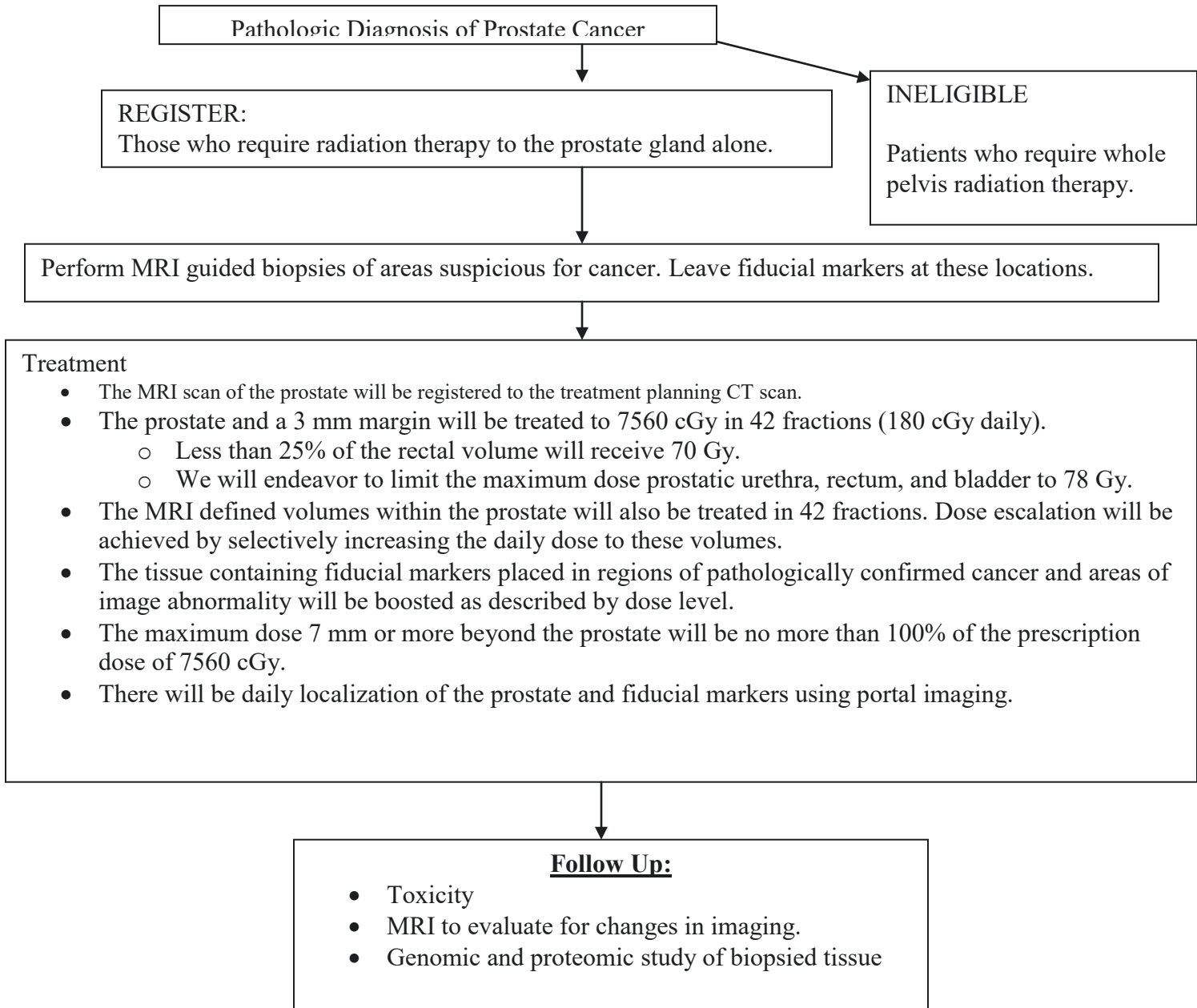


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1.0 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary:

To determine the maximum tolerated dose (MTD) of external beam radiation to regions of interest within the prostate based on MRI.

1.1.2 Secondary:

1.1.2.1 To correlate radiation response and/or toxicity with genomic and proteomic analyses.

1.1.2.2 To evaluate long-term effects and toxicity following selective intra-prostatic dose escalation.

1.2 BACKGROUND AND RATIONALE

1.2.1 Intensity modulated radiation therapy (IMRT)

Several studies have established that escalating doses of external beam radiation therapy improves biochemical disease free survival in prostate cancer. These gains in biochemical disease free survival, however, come with the potential risks of long-term toxicity with dose escalation.

Intensity modulated radiation therapy (IMRT) is a newer form of radiation dose delivery that allows for delivery of high doses of radiation with rapid drop off of dose beyond the target. This combination of factors allows targeted dose escalation while decreasing or maintaining the amount of dose to a given volume of normal tissue.

In IMRT the physician defines the target volume as well as the dose constraints on normal tissue. The treatment planning computer then does “inverse planning” to generate an acceptable plan that meets the target coverage and normal tissue dose constraints. If the physician remains unsatisfied with the plan, the priorities of tumor coverage and normal tissue limits can be adjusted and the plan re-generated.

Each IMRT system’s inverse planning algorithm is proprietary. In broad terms, however, the planning system simply attempts thousands of different plans until an acceptable one is found to present to the physician.

A consequence of this method is that IMRT systems produce plans with doses far in excess of the prescribed dose. These regions are known as “hot spots.” Randomly placed hot spots of 20% within the target volume are common. Nevertheless, excellent clinical results have been obtained with this system.

Evolving research initiatives in the Radiation Oncology Branch (ROB) and the Radiation Oncology Sciences Program (ROSP), NCI, depend upon the

availability of tissue samples from patients receiving radiotherapy. The tissue *acquired* in this preliminary effort is critical to the expansion of our knowledge of radiation induced gene and protein expression profiles, and will potentially generate novel hypotheses for molecular therapeutic strategies.

1.2.2 Dose Escalation In Prostate Cancer

In a study of 301 patients, Pollack et al demonstrated that doses of 7800 versus 7000 cGy produced significantly improved failure free survival in intermediate to high risk patients (70 versus 64%, $p=0.03$).[2]

Zeitman et al have recently reported on a trial comparing 7920 versus 7020 cGy (actually cobalt Gray Equivalent dose) in patients with prostate cancer treated with a proton boost. The five-year biochemical failure rates were 37.3% for the conventional dose group and 19.1% for the high dose group ($p=0.00001$).[3]

Increased toxicity accompanied dose escalation in Pollack's experience. This toxicity was reduced if less than 25% of the rectal volume was irradiated to 7000 cGy.[2]

Understanding the need to dose escalate while minimizing the amount of normal tissue irradiated, several investigators have explored dose escalation with IMRT.[4]

IMRT has been used by Zelefsky et al to dose escalate to doses of 86.4Gy to the entire prostate gland. In their experience with 772 patients and a median follow-up of 24 months, less than 5% developed acute Grade 2 rectal toxicity. Only one experienced urinary retention (Grade 3). Eleven patients (1.5%) developed late Grade 2 rectal bleeding. Four patients (0.1%) experienced Grade 3 rectal toxicity requiring either one or more transfusions or a laser cauterization procedure. The 3-year actuarial PSA relapse-free survival rates for favorable, intermediate, and unfavorable risk group patients were 92%, 86%, and 81%, respectively. IMRT has become the standard mode of conformal treatment delivery for localized prostate cancer at Memorial Sloan Kettering.[5]

1.2.3 Fraction Size and Dose-Volume Limits In Prostate Cancer

Based on laboratory research in classical radiation and the results of clinical trials, Fowler et al have proposed that using larger doses of radiation with each fraction may produce greater local control in prostate cancer. They actually suggest that this use of larger fraction size without dose reduction may be possible without increased late toxicity. [6, 7]

However, this theoretical work is belied by the results of RTOG study 9406. Results of this study demonstrate that doses of 7400 cGy in 200cGy daily

fractions produce less than 5% grade 3 acute toxicity and 2% late grade 3 toxicity. Late toxicities were halved when 180 cGy daily fractions were used.[1]

In the current study, it may be possible to have the best of both worlds. IMRT treatment as proposed should allow the benefits of hypofractionation while maintaining the lower risk of late toxicities by ensuring that normal tissues continue to be treated at 180 cGy per day.

Patient-based self-assessment questionnaires provide valuable toxicity endpoints. The Expanded Prostate Cancer Index Composite (EPIC) is a robust prostate cancer health related quality of life instrument that measures a broad spectrum of bowel symptoms, and has been validated in patients receiving radiotherapy. 28. The American Urological Association (AUA) Symptom Score and The Sexual Health Inventory for Men (SHIM) questionnaires address the significant quality of life issues of urinary functioning and erectile dysfunction respectively.

On the present study, no volume 4 mm beyond PTV1 will be allowed to receive a dose beyond 100% of the prescription dose. This 100% at 4 mm dose constraint is derived from the RTOG 9406 experience. That study of three dimensional conformal therapy mandated 5 to 10 mm uniform margins on the prostate. Commonly, 7 mm margins were used. Consequently maintaining a dose of no more than 100% at a distance of 4 mm from PTV1 (which is 3 mm from the prostate) should be very well tolerated.

PTV2 will be defined as regions of signal abnormality (plus a 2 mm margin) on MRI that do not have a pathologic confirmation of disease. Dose will be escalated by protocol (see section 3.1.2).

PTV3 will be defined as regions of signal abnormality (plus a 2 mm margin) on MRI that have pathologic confirmation of disease. Dose will be determined by protocol. If the patient previously had at least a sextant biopsy with documentation of the location of the positive cores, this information may be used to define a PTV3. The maximum protocol dose to PTV3 on this study is approximately 150 Gy. This is similar to the prescription dose of 145 Gy used with low dose rate (LDR) iodine 125 (I^{125}) brachytherapy. LDR brachytherapy has been widely utilized to treat low risk prostate cancer with acute and late morbidity broadly comparable to external beam radiation therapy.

While the prescription dose of 145 Gy covers the prostate in brachytherapy, doses near each I^{125} seed are necessarily far higher. Consequently, it appears that small volumes of prostate can tolerate doses far in excess of 145 Gy without excessive toxicity.

Certainly, between brachytherapy and external beam irradiation there are major differences in dose deposited per unit time and total treatment time. These differences make direct dose comparisons difficult. Nonetheless, the experience with brachytherapy does provide a reasonable ceiling in the current dose escalation study.

Furthermore, brachytherapy has demonstrated that urethral toxicity may occur with higher doses to the urethra.[8] For this reason, doses to the prostatic urethra, as defined by the attending physician, will be limited to 78 Gy (approximately the maximum dose allowed in the Pollack and RTOG 9406 experience).

As per the Pollack experience, less than 25% of the rectal volume will be irradiated to 7000 cGy.[2] Maximum dose to the bladder and rectum will be limited to 7800 cGy.

1.2.4 MRI and the Detection of Prostate Cancer

At present there are no imaging techniques that can accurately delineate tumors within the prostate gland. Transrectal ultrasound, although in wide use for guiding biopsies, is not sensitive for the detection of prostate cancer despite the advent of color Doppler and ultrasound contrast agents.[9, 10] Computed tomography is also insensitive for localized prostate cancer.[11] PET scanning with Fluorodeoxyglucose (FDG) is limited by artifacts related to the urinary bladder and by relatively low avidity of FDG for prostate cancer.[12, 13] While other PET agents are under investigation, none has yet emerged as clearly superior to any other.[14]

MRI offers a 3D dataset, multiple imaging planes, and unparalleled soft tissue resolution, making it the modality of choice for imaging the prostate gland. MRI has been shown to provide better visualization of the prostate and surrounding structures than either ultrasound or CT.[15] T2-weighted scans depict the normal peripheral zone as high in signal and tumors are depicted as relatively low in signal, a characteristic appearance that can detect 60 to 80% of prostate cancers, but that is limited by non-specificity, with prostatitis and hyperplasia mimicking tumor. Evidence of extraprostatic spread of tumor includes hypointense stranding in the periprostatic fat, obliteration of the rectoprostatic angle, or clear-cut extracapsular extension. Staging accuracies of extracapsular extension for high field strength MR images are as high as 82% to 88% in single institutional series.[16-18]

In patients with known prostate cancer, based on our experience with ongoing protocol NCI #02-C-0207E, we have been able to identify and biopsy regions of signal abnormality by MRI. In 50% of patients these biopsies have yielded specimens containing prostate cancer.

This yield, while impressive for an experimental system in the early stages of clinical development, is suboptimal. During the course of this protocol, in addition to standard MR imaging sequences, we will continue to obtain and experiment with novel MR sequences to give better delineation of prostate cancer. Target volumes, however, will be defined by pathologic correlation with imaging as described above.

1.2.5 The 'APT-MRI' system

In collaboration with Department of Biomedical Engineering at Johns Hopkins we have developed a system that provides transrectal needle access to the prostate while a patient is imaged inside of a 'closed' scanner. This system, called the APT-MRI system (Access to Prostate Tissue under MRI-guidance), will be utilized in this study to acquire needle biopsy tissue in accurate reference to DCE-MRI images.

The method is very similar to transrectal ultrasound guided biopsy of the prostate, except that it is applicable within a closed high-field MRI scanner. In canine studies, accurate needle placement in a variety of clinical applications (e.g. biopsy, injections, and seed placement) were demonstrated.[19] This system was adapted to clinical use and investigated for feasibility, tolerability, and needle targeting accuracy under protocols 03-C-0190 and 02-C-0167.

Clinical results to date show that the APT-MRI system is safe, well tolerated, and can target prostatic sites with millimeter accuracy.[20] We used the 'APT-MRI' system to place gold fiducial markers within the prostate gland in patients with localized prostate cancer in order to assess not only needle placement accuracy, but also the accuracy with which the tissue itself was targeted (i.e. leaving a permanent marker allows for measurement of the impact of tissue deformation, produced during needle insertion, on targeting accuracy). Subsequently, the system was also used for four 1.5T MRI-guided prostate biopsy procedures in three patients.

The mean MR procedure duration was 72 minutes and was well tolerated. Using axial MR images, needle and marker placement errors were assessed (see figures 1& 2). The mean needle placement accuracy was 1.9 mm for the fiducial marker placement studies and 1.8 mm for the biopsy procedures. The mean fiducial marker placement accuracy was 4.8 mm and the mean transverse fiducial marker placement accuracy was 2.6 mm. The gold fiducial markers were subsequently used to assess daily setup errors and off-line organ motion during a standard course of external beam radiation therapy for prostate cancer.

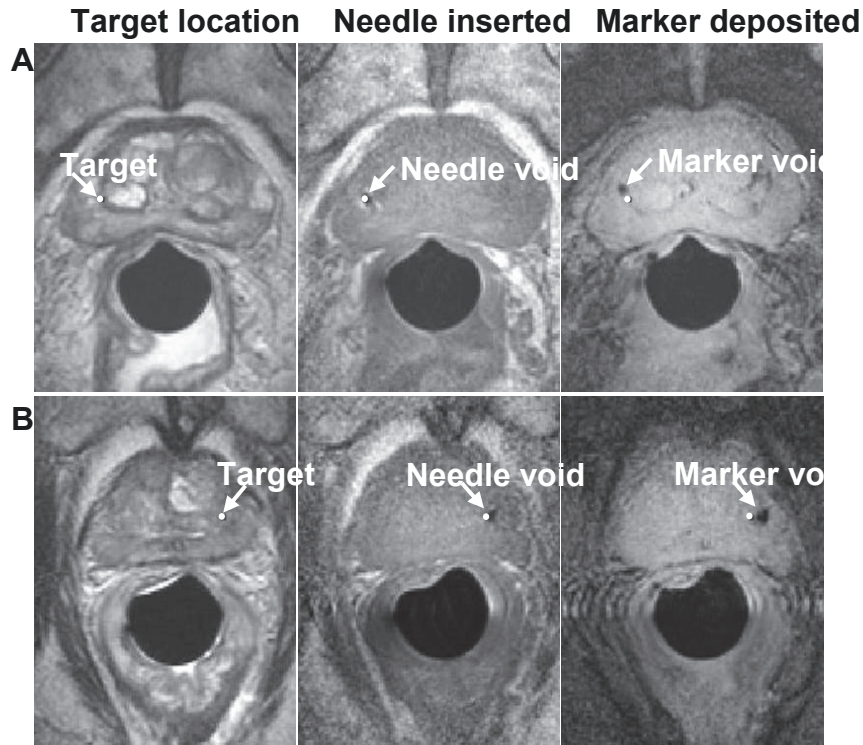


Figure 1: Targeting, needle, and fiducial-marker visualization images. Images from two patients (**Rows A and B, respectively**), show images acquired during the fiducial-marker placement procedure. **Column 1:** Targets are selected on axial, T2-weighted fast spin-echo images. The site pre-selected for targeting is represented by a white dot in all images. **Column 2:** The needle tip void is visualized in axial, T1-weighted fast spin-echo images. **Column 3:** The marker void is visualized on axial, T2*-weighted gradient-echo images. Note that there is minimal tissue motion throughout each procedure.

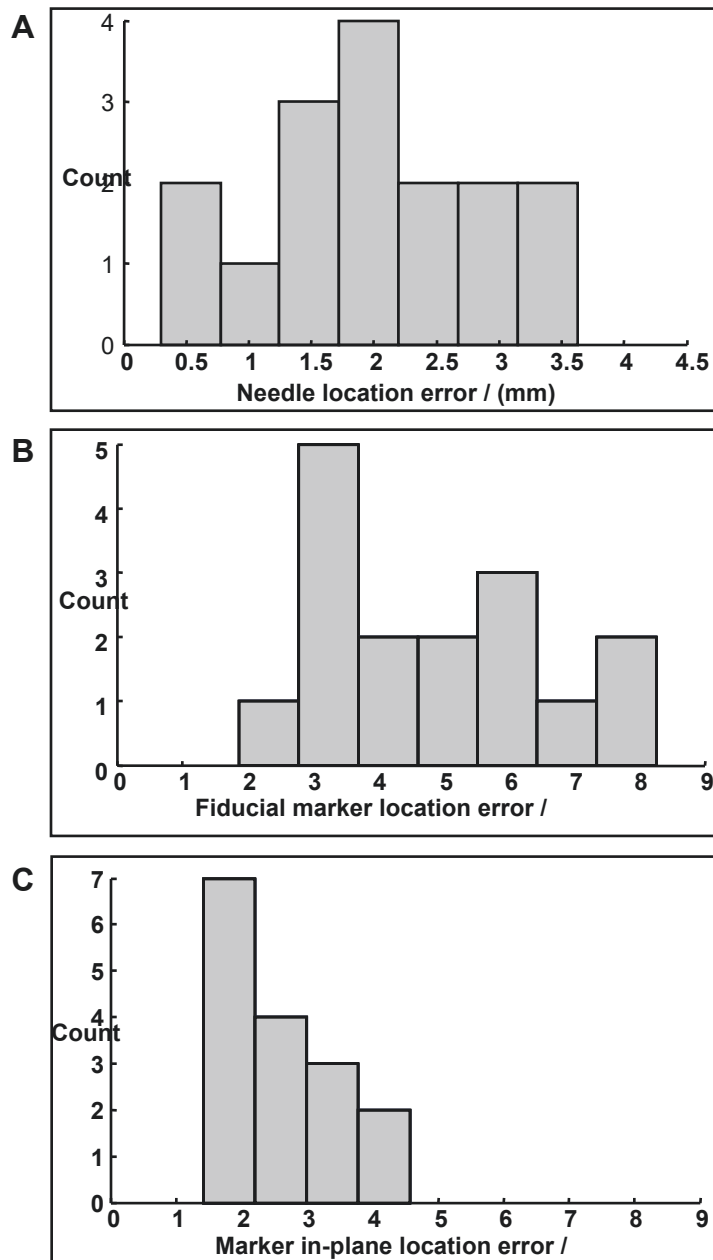


Figure 2: Needle and fiducial-marker placement accuracy. Error histograms show needle tip location errors (**Panel A**), fiducial marker location errors (**Panel B**), and fiducial marker in-plane location errors (**Panel C**) for all 16 gold fiducial markers placed. Mean placement errors for each are 1.9 mm, 4.8 mm, and 2.6 mm, respectively. Because tissue core biopsies are typically 1.5 cm long, the last measure, fiducial marker in-plane placement error, is the best predictor of tissue acquisition accuracy.

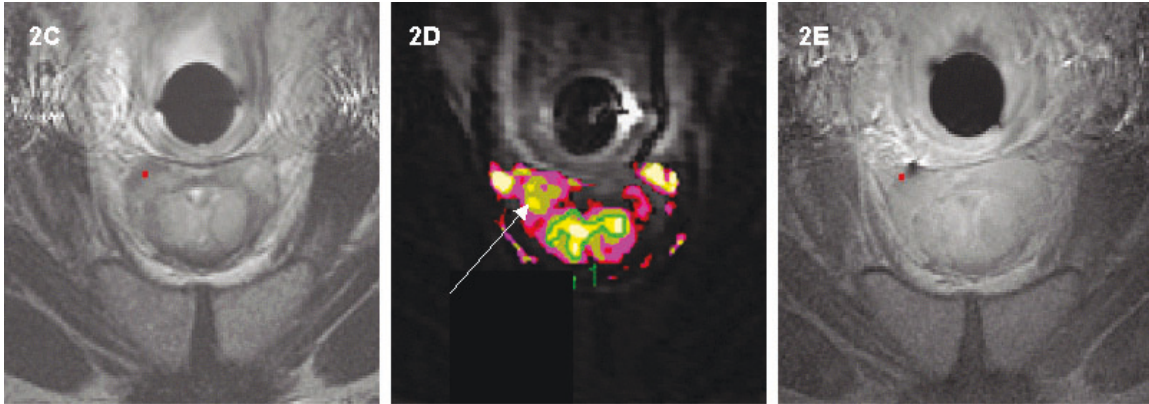


Figure 3: A case example whereby T2W FSE images (2C) shows a suspicious lesions in the peripheral zone which was targeted for biopsy (red dot). Dynamic contrast MRI color-coded for contrast kinetics (2D) shows normal activity in the central gland and neurovascular bundles, and activity suspicious of malignancy in the peripheral zone (arrow) corresponding to the targeted site. The biopsy needle can be visualized on axial images (2E - signal void) prior to tissue acquisition in close proximity to the intended target (red dot).

1.2.6 Fiducial Markers

Using MRI for anatomic guidance and visualization, between 2 and 6 gold fiducial markers will be placed within the prostate of patients with cancer prior to external beam radiotherapy. Our experience with ongoing protocol 03-C-0190C has demonstrated that these fiducial markers can be accurately placed using MRI guidance (see figure 3).

While placement of the gold markers has no direct therapeutic benefit for the patient per se, intraprostatic fiducial markers (placed under ultrasound) have shown value in assessing daily setup errors and off-line organ motion during external beam radiation therapy for prostate cancer.[21-23] These markers can also be utilized to aid in CT-MRI fusion[24] and result in better target delineation for treatment planning as well as daily localization.

IMRT with its very tight margins is at high risk of missing tumor beam as a result of organ motion and inaccurate patient positioning. Current measures, such as patient immobilization devices and laser-tattoo alignments, do not address prostatic motion relative to bony landmarks. Variations in bladder and rectal filling have been shown to affect prostate position within the pelvis, to an extent which may require field adjustments during the course of radiotherapy.[25] Since the rectum tends to become progressively less distended during a course of pelvic radiotherapy (mean decrease in diameter 1.5cm), the predominant prostatic motion is in the posterior and inferior direction. In one study 11% of patients showed an inferior shift of the prostate of more than 1cm and 30% showed a posterior shift of more than 1cm.[22]

Portal x-ray imaging is a technique used to monitor the accuracy of beam isocenter positioning relative to bony landmarks during radiotherapy. Since the prostate is not visible on portal imaging, radiopaque fiducial markers are surrogates for organ localization in portal images.[26] Studies show that the degree of possible migration of the fiducial markers is negligible and within the limits of accuracy of CT measurements (2mm).[27]

As prostate motion is the major source of error in radiation treatment delivery[21], some investigators have recommended that radio-opaque markers be placed in the prostate prior to the start of radiotherapy.

1.2.7 Genomic Analysis

Serum and tissue will be stored in the Radiation Oncology branch. Future genomic and proteomic analysis may be performed as in 3.2.3.

2.0 Eligibility Assessment and Enrollment

2.1 ELIGIBILITY CRITERIA

2.1.1 *Inclusion Criteria*

- 2.1.1.1 ECOG performance status of 0,1, or 2
- 2.1.1.2 Pathology report confirming adenocarcinoma of the prostate
- 2.1.1.3 Risk of lymph node metastasis less than 10% as defined by the Partin tables (see appendix I)
- 2.1.1.4 Tumor visible on MRI
- 2.1.1.5 No prior surgery, radiation, or chemotherapy for prostate cancer.
- 2.1.1.6 Age greater than 18 y/o and less than 90 years old.

2.1.2 *Exclusion Criteria*

- 2.1.2.1 Cognitively impaired patients who cannot give informed consent.
- 2.1.2.2 Patients with metastatic disease.
- 2.1.2.3 Contraindication to biopsy
 - Bleeding disorder
 - PT/PTT \geq 1.5 times the upper limit of normal
 - Platelets \leq 50K
 - Artificial heart valve
- 2.1.2.4 Contraindication to MRI
 - Patients weighing >136 kgs (weight limit for the scanner tables)
 - Allergy to MR contrast agent
 - Patients with pacemakers, cerebral aneurysm clips, shrapnel injury or implantable electronic devices.
- 2.1.2.5 Pre-existing and active prostatitis or proctitis.

2.1.2.6 Other medical conditions deemed by the PI or associates to make the patient ineligible for protocol investigations, procedures, and high-dose external beam radiotherapy.

2.2 PRE-TREATMENT RESEARCH ELIGIBILITY EVALUATION

2.2.1 Clinical Evaluation

- History and Physical Examination.
- Pathology report confirming adenocarcinoma of the prostate (outside report acceptable for study entry; pathology review by NIH to be done prior to treatment initiation).

2.2.2 Laboratory Evaluation

- PSA
- PT/PTT
- CBC

2.3 PATIENT REGISTRATION

Authorized staff must register with the Central Registrar's Office an eligible candidate within 24 hours of signing the consent. A registration checklist from the Web site

(<http://home.ccr.cancer.gov/intra/eligibility/welcome.htm>) must be completed and faxed to the Central Registrar's Office at 301-480-0757. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

3.0 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

3.1.1 Overall Trial Design

Patients with prostate cancer who have no evidence of metastasis will be eligible for this study. This phase I trial will use intensity modulated radiation therapy (IMRT) to deliver escalating doses of external beam radiation therapy to regions of histologically confirmed prostate cancer while regions of signal abnormality on MR imaging without pathologic confirmation will receive intermediate doses.

Anatomic MRI and MR biological images will be obtained. Tissue will be acquired from sites of interest, with biopsy locations precisely translated (co-registered) to an MR image of reference. A fiducial marker (gold seed) will be left at the biopsy site as a fiducial marker to direct future radiation therapy. The patient will undergo a standard CT simulation for radiation therapy treatment planning. The MR and CT images will be fused. Areas of pathologically confirmed malignancy will undergo dose escalation as

described below. Areas of image abnormality that could not be biopsied or were without definite pathologic evidence of malignancy will be given intermediate doses. The remainder of the prostate gland will receive standard dose (as per the Radiation Therapy Oncology Group (RTOG) 9406 study) 7560 cGy in 180 cGy daily fractions.[1] Treatments will occur at the NCI, Department of Radiation Oncology on weekdays. There will be no treatments on weekends or holidays.

3.1.2 Dose Escalation

The primary objective of this study to determine the MTD of radiation to regions of interest (as determined by MRI and pathology) within the prostate gland.

As random “hot spots” of radiation are not uncommon with IMRT (see 1.2.1), we will begin at a very conservative dose of 125% and escalate as follows in cohorts of 3 patients each.

Cohort	Prescription Dose to Areas of Path Confirmed Tumor*	Prescription Dose to Areas of Image Abnormality Only*	Max Dose Allowed Beyond PTV1 + 4mm*
I	125%	115%	100%
II	138%	125%	100%
III	150%	138%	100%
IV	165%	150%	100%
V	180%	165%	100%
VI	200%	180%	100%

*The reference dose for calculation of these percents is 7560 cGy

3.1.3 Criteria for Dose Escalation

Each dose cohort will accrue 3 patients. If there are no DLT in 3 patients then patients will be accrued to the next dose level. If two or more patients experience a DLT then the MTD will be exceeded and the prior lower dose cohort will be considered the MTD. If a DLT occurs in one of three patients then an additional 3 patients will be accrued to that dose level. If fewer than 2 of 6 patients experience an acute DLT in the expanded cohort then patients will be accrued to the next dose cohort. If 2 or more of 6 patients experience a DLT then the MTD will be exceeded and the prior, lower dose cohort will be considered the MTD.

For the purposes of dose escalation, DLT will be evaluated at 12 weeks after completion of radiation therapy. The course of radiation therapy lasts 7 to 8 weeks or 42 fractions 5 days per week. For patients in the next (higher) dose cohort, escalation of the total dose will not occur until after fraction 34 of the

radiation. Therefore, we will allow the accrual of up to 3 patients in the next dose cohort into the study before currently enrolled patients have reached the 12 week endpoint. This will be allowed as long patients at the current dose cohort have been followed for a minimum of 7 weeks.

3.1.4 Definition of Dose Limiting Toxicity (DLT)

An acute DLT will be defined as RTOG grade 3 or greater, acute GI or GU toxicity (see appendix IIA) within 3 months after the completion of radiation. Thus, accrual to an escalated dose cohort may need to be delayed so that all 3 patients in the current cohort are followed for 2 months. Given that the volume of normal tissue irradiated to standard dose or higher will be substantially limited, late toxicity is less of a concern than acute toxicity.

3.1.5 Definition of Maximum Tolerated Dose (MTD)

The primary objective is to estimate the MTD of external beam radiation that results in limiting acute toxicity. The MTD is defined as the dose level immediately below the dose level at which 2 or more in a cohort of either 3 or 6 patients experienced a DLT attributed to radiation therapy. If DLT does not occur at the highest dose level the protocol will be amended to escalate by 10% in cohorts of 3 patients each with the standard 3-6 dose escalation procedure.

3.2 PROTOCOL ADMINISTRATION

3.2.1 MR Imaging Guidelines

In all patients, conventional anatomic imaging (Fast spin echo T2 weighted scans) in the axial and coronal oblique planes will be obtained for research purposes to define the extent of the tumor. An endorectal coil may be indicated for prostate exams.

Following conventional anatomic imaging, one or more of the following research biological imaging tests will be performed. Examples include but are not exclusive to:

a) MR Spectroscopic Imaging (MRSI)

Using standard FDA approved spectroscopy software (General Electric Medical Systems, Milwaukee, WI), this will be performed using multiple voxels at multiple slices ("multivoxel-multislice MR spectroscopy") which will generate a spectroscopic map of the area of interest reflecting the relative concentrations of various metabolites in the hydrogen resonance spectrum including citrate, choline, creatine, choline and lipids. This procedure may require approximately 30-45 minutes of scanning.

b) Dynamic Contrast Enhanced MRI

This imaging study uses 1mmol/kg of an FDA approved Gadolinium chelate administered slowly by intravenous injection. Serial 3D dynamic enhanced MRI may be performed through the area of interest over a period of approximately 10 minutes. These data will be sent electronically to an independent workstation where a pixel by pixel time-signal intensity curve will be generated. This data will be automatically fit to a two compartment pharmacokinetic model using a custom designed image processing algorithm which will be used to generate semiquantitative parameters reflecting flow ("A") and vessel permeability (k_{ep}). These parameters will be used to create color encoded maps which reflect the vascular flow and permeability of various regions.

c) BOLD

To accomplish this, the patient will first breathe room air via a regulated and non-magnetic tank set at 10L/min for 5 minutes via a specially designed breathing apparatus designed by Hugh Preas, M.D. of the Anesthesia Department. This breathing apparatus consists of a mouth piece and a clamp is place on the nose. It is non-invasive, and the patient can let go of the mouth piece if they find it uncomfortable.

Following this baseline study, the inhaled gas will be switched to regulated medical grade carbogen (5% carbon dioxide and 95% oxygen) in non-magnetic tanks administered at 10-15L/min for 7 minutes. This will improve the oxygenation of tissue by a combination of hyperoxia due to the high oxygen content and vasodilation due to carbon dioxide. Following carbogen inhalation the patient will be switched back to the room air at prior rates for 5 minutes. Images will be analyzed by measuring the difference in signal between the room air and carbogen scans and color maps reflecting per cent change in signal intensity will be generated for comparison.

d) OTHER Sequences

Other MRI sequences may be obtained. However, these other sequences will involve novel pulse sequences or post-processing of image data that will be transparent to the patient and will not require any additional procedures to be performed.

Of note, given the time required to perform and analyze these sequences as well as the length of the biopsy procedure, patients may have the target imaging with various high resolution sequences done at a separate time from the biopsy itself.

3.2.2 Tissue Collection

3.2.2.1 General co-registration guidelines

Co-registration of the biopsy site to an MRI image will be accomplished by one of the following options: 1) real-time MR guidance of the biopsy procedure, 2) placing fiducial markers visible on MRI to identify sites selected for future biopsy, 3) fusing images from CT or Ultrasound-guided biopsy procedures to MR images, 4) repeat MRI immediately after a biopsy procedure to identify needle tracts.

Tissue will be collected with standard biopsy procedures (outlined below). NSAIDS should be discontinued one week prior to a biopsy procedure unless it is deemed unsafe or violates with the treatment protocol. Note that a separate consent specific to each biopsy procedure will be obtained.

3.2.2.2 Prostate biopsy

Needle biopsies will be performed in collaboration with surgeons from the Urologic Oncology Branch-NCI, and Radiologists from the Clinical Center-NIH. During each procedure, 2-10 samples will be obtained using 14-18 gauge tru-cut needles.

Biopsies will be performed according to standard techniques as follows. Patients undergo antibiotic prophylaxis with a quinolone antibiotic for one or two days before biopsy and the morning of biopsy. If the patient is known to be allergic to this antibiotic or if they experience an allergic reaction to it, a different one, such as Bactrim, will be prescribed. A rectal enema is self-administered. Patients void and then are placed in the prone position or in the left- or right-lateral decubitus position. A transrectal ultrasound or MRI probe (custom designed coil, approved by NMR Center Research Safety Subcommittee) is inserted and imaging measurements of the prostate obtained. After initial imaging is obtained, transperineal (or transrectal) introduction of 10-20 cc 1% lidocaine or 10cc of 0.25% bupivacaine is administered along the paraprostatic neurovascular bundle and the tip of the seminal vesicle. After 3 minutes of dwell time, transperineal (or transrectal), targeted prostate biopsy is performed as directed by imaging and 3-D spatialization (i.e. in the x,y,z coordinates). The patient recovers in the supine position and is allowed to ambulate shortly thereafter with a normal mean blood pressure. The patient is required to void without difficulty prior to discharge. Prostate biopsy is extremely well tolerated with complications occurring in 1% due mostly to infection, which can be treated in most cases with parenteral or enteral antibiotics as adjudged by the clinician.

3.2.2.3 Tissue Handling

Dr. Kaushal should be notified prior to specimen collection. Unless otherwise directed by Dr. Kaushal, samples will be delivered to Building 10, RmB3/43, phone 496-5457.

Samples will be divided at the time of the procedure. Half will be immediately fixed in formalin and submitted to the Laboratory of Pathology, NCI, for histopathological analysis. The remaining tissue will be placed in freezer vials and immediately frozen in liquid nitrogen.

3.2.2.4 Tissue Analysis

A diagnostic pathological evaluation will be performed on the specimens in collaboration with the laboratory of pathology – NCI. Supplementary tests, including but not exclusive to immunohistochemistry and counts of microvessel density, may be performed in a pilot exploratory fashion at the discretion of the principal investigator.

Tissue samples may then be processed for microarray testing. RNA will be isolated and pooled from the cell population of interest. Depending on the number of cells captured, amplification strategies may be explored. Using the total RNA, probes will be prepared and hybridized to a human microarray chip. Microarray analysis will then proceed with the mAdb analysis tools available to NIH investigators (nciarray.nci.nih.gov). Other software will be used as needed.

Tissue specimens collected in the course of this research project may be banked and used in the future to investigate new scientific questions related to this study. However, this research may only be done if the risks of the new questions were covered in the consent document.

No germline mutation testing will be performed on any of the samples collected unless the patient gives separate informed consent. Tests will be pilot studies related to the Branch's work on such topics as molecular imaging, molecular profiling, and novel molecular therapeutics. If any research tests are considered to be themselves of more than minimal risk to the patients, separate permission will be requested from the IRB to perform that test, and a new consent will be obtained.

At the completion of the protocol, the investigator will dispose of all specimens in accordance with the environmental protection laws, regulations and guidelines of the Federal Government and the State of Maryland.

Any loss or unintentional destruction of the remaining samples will be reported to the IRB.

3.2.3 Radiation Therapy

3.2.3.1 Treatment planning

PTV1 will be defined as the prostate with a 3 mm uniform margin. The prescription dose to PTV1 will be 7560 cGy in 180 cGy daily fractions. Consistent with the RTOG 9406 data, no volume 4 mm beyond PTV1 will be allowed to receive a dose beyond 100% of the prescription dose. This will be the highest priority constraint for treatment planning. Lesser doses to PTV2 and PTV3 will be accepted in order to maintain this constraint.

PTV2 will be defined as regions of signal abnormality (plus a 2 mm margin) on MRI that do not have a pathologic confirmation of disease. Dose will be escalated by protocol (see section 3.1.2).

PTV3 will be defined as regions of signal abnormality (plus a 2 mm margin) on MRI that do have pathologic confirmation of disease. Dose will be determined by protocol. If the patient previously had at least a sextant biopsy with documentation of the location of the positive cores, this information may be used to define a PTV3. In this case, the physician will determine the volume.

If indicated, the seminal vesicles may also be contoured and treated. When indicated, the seminal vesicles may be treated to 5400 cGy in 180 cGy.

3.2.3.2 Summary Of Dose Constraints:

Highest Priority:

- PTV1 will be defined as the prostate with a 3 mm uniform margin. The prescription dose to PTV1 will be 7560 cGy in 180 cGy daily fractions. No volume 4 mm beyond PTV1 will be allowed to receive a dose beyond 100% of the prescription dose.
- The prostatic urethra, as defined by the attending physician, will attempt to be limited to 7800 cGy.
- Maximum dose to the rectum and bladder will also attempt to be limited to 7800 cGy.
- Less than 25% of the rectal volume will be irradiated to 7000 cGy.

Secondary Priority:

- PTV2 and PTV3 will be taken to full dose as per protocol.
- No more than 40% of the bladder will receive more than 6500 cGy.

3.2.3.2 Radiation Treatment

Patients should begin their radiation treatment once pathology is available. In general patients will receive external beam radiation in the NCI Radiation Oncology Clinic daily, Monday – Friday except holidays.

3.3 TREATMENT MODIFICATIONS

Modifications to the radiation treatment will be discussed with the Principal Investigator or Study Chairperson. Isocenter adjustments will be performed for prostate motion greater than 5 mm. In each dose cohort, the attending physician may accept a final plan that delivers 107 to 93% of the prescription dose to PTV 1-3. Larger deviations will require prior approval of the PI.

3.4 ON-STUDY EVALUATION

3.4.1 Pre-Procedure (baseline)

- Informed consent obtained
- Clinical evaluation
 - History and physical exam
 - Vital signs
 - Pathology report confirming adenocarcinoma of the prostate
- Laboratory evaluation
 - PSA
 - PT/PTT
 - CBC
- EPIC (Appendix IIIC)
- AUA Symptom Score (Appendix IV)
- Sexual Health Inventory for Men (SHIM) (Appendix V)

3.4.2 Biopsy & Fiducial Marker Placement

- See Appendix III for MRI- Guided biopsy and FM data form
- Post fiducial marker placement MRI's may be performed to evaluate for marker migration

3.4.3 Radiation Treatment Phase

- Weekly AP (or PA) and lateral port films
- The following acute rectal toxicity endpoints will be measured.
 - RTOG acute toxicity grading- GI & GU (Appendix IIA) weekly and at completion of therapy

3.4.4 Post Active Treatment Evaluation (follow- up)

- Upon completion therapy, patients will be evaluated at 2, 4, 8, and 12 weeks for acute effects of radiation therapy. Patients will be evaluated at 6, 9, 12, 18 and every 6 months afterward for late effects until 36 months.
- Follow-up visits will include:
 - A directed history and physical examination,
 - PSA evaluation
 - Rectal toxicity assessment including:

- RTOG acute toxicity grading- GI & GU(Appendix IIA)
 - RTOG Late toxicity grading- GI & GU (Appendix IIB)
 - EPIC (Appendix IIIC)
 - AUA Symptom Score (Appendix IV)
 - Sexual Health Inventory for Men (SHIM) (Appendix V)
-
- Follow-up MRI may be obtained after completion of therapy to better delineate the time of course of signal change after radiation therapy.
 - Patients may volunteer for additional imaging and tissue acquisition procedures if deemed desirable by the PI or study chairperson.

3.5 CONCURRENT THERAPIES

This study allows imaging and tissue procurement in localized prostate cancer patients without metastasis. Usually, such patients do not receive hormonal or chemotherapy. Some patients do receive hormone therapy prior to being seen by a radiation oncologist. Such patients will remain eligible for this study. However, it is preferred that they discontinue hormone therapy while receiving radiation.

3.6 SURGICAL GUIDELINES

None other than those required for standard biopsy procedures. Where clinically indicated, biopsies will be performed under appropriate analgesia, local/systemic anesthesia and/or conscious sedation with patient monitoring in compliance with hospital standards, no general anesthesia will be administered for research purposes only. Only biopsies that are “minimal risk” and do not require general anesthesia will be performed for research purposes only. Please refer to section 3.2.2. for details on the biopsy procedures.

3.7 RADIATION THERAPY GUIDELINES

Radiation Therapy is part of the primary protocol treatment and is therefore included in section 3.2.3

3.8 OFF STUDY CRITERIA

3.8.1 Patients may be taken off study for the following non-medical or administrative reasons:

- Patient refuses the procedure or further treatment
- It is deemed in the patient’s best interest as determined by the PI.
- Serious protocol violation as determined by the PI.

3.8.2 *Development of a concurrent serious medical condition that precludes the completion of fiducial marker placement, radiation therapy or follow-up.*

3.8.3 *Tumor progression (if occurs during treatment, at the end of radiation therapy unless the completion of local therapy is not indicated)*

3.8.4 *Initiation of cytotoxic chemotherapy (if occurs during treatment, at the end of radiation therapy unless the completion of local therapy is not indicated)*

3.8.5 *Development of a concurrent serious medical condition during active treatment and not attributable to therapy that precludes the completion of active treatment.*

3.8.6 *The completion of 36 months (3 years) follow-up.*

3.9 POST-STUDY EVALUATION

- At the time a patient comes off study the reason for withdrawal should be documented.
- The patient should be registered off- protocol by completing the Off Study/ Death Notification Form available from the web site (<http://home.ccr.cancer.gov/intra/eligibility/welcome.htm>) and faxing it to the Central Registrar's Office at 301-450-0757.

4.0 SUPPORTIVE CARE

These procedures may require supportive care including nursing care, local anesthetic, analgesics, anti-emetics, and antibiotic prophylaxis. Please refer to section 3.2.2.2 – 3.2.2.3 for details. In the event that a patient has a reaction (allergic) to the contrast agent or medications, all appropriate medical measures will be taken.

The most common acute side effects of radiation therapy for prostate cancer, urethritis, cystitis and proctitis, may be treated with medications consistent with the standard of practice in the radiation oncology community. It is anticipated that a minority of patients may require short-term in-patient care for problems related to this protocol, namely an inability to void immediately post-op. In such circumstances, patients will be admitted to the Clinical Center under the care of the Urologic Oncologist. Medications should be listed in the patient's records.

5.0 DATA COLLECTION AND EVALUATION

5.1 Data Collection

- Clinical data and acquired samples/images will be recorded in a NCI CCR database.
- Clinical data collection will include: demographic information, pathologic diagnosis, clinical stage, PSA values, history including concurrent therapies, time of biopsy, locations of biopsies, pathology reports of biopsies, dose of radiation delivered, and toxicity assessment.
- Tissue experiments to be performed are pilot and preliminary in nature. Data from assays run at the NIH will be collected in laboratory notebooks, and the NCI online microarray database.
- MRSI and dynamic MRI measurement along with corresponding sites of tissue acquisition will be digitally archived and processed using computer software in the Radiology department of the Clinical Center, NIH, and the Radiation Oncology Branch, NCI.

5.2 Response Criteria

Response of tumor will be determined by tracking serum PSA levels. Three consecutive rises of the PSA post-treatment will define disease recurrence. The time of disease recurrence will be back-dated to the first rise in PSA. This methodology is as prescribed by the American Society of Therapeutic Radiation Oncology (ASTRO.)

5.3 Toxicity Criteria

- Acute toxicities will be evaluated by the CTC, Version 3.0. (<http://ctep.info.nih.gov>).
- We will also utilize the RTOG acute and Late toxicity GI/ GU scales as in appendices II A & B

5.4 Statistical Section

This is a phase I study to determine the maximum tolerated dose (MTD) with MRI-guided radiation dose escalation to regions of interest within the prostate gland. The dose cohorts and MTD are defined in Section 3.1.1. With this design, the probabilities of dose escalation are 0.91, 0.49, 0.17, and 0.03 if the probability of a DLT is 0.1, 0.3, 0.5, and 0.7, respectively.

Secondary analyses include (i) evaluating the frequency of late term toxicities, and (iii) correlating radiation response and /or toxicity with genomic and proteomic analyses. We will tabulate the frequency of late term toxicities. We will analyze differences in gene expression between responders and non-responders as well as between patients with toxicity and without toxicity by conducting, on a gene by gene basis, two-sample t-tests at the 0.001 level. We will also conduct permutation tests to test for overall differences in gene expression between these patient groupings. All secondary analyses will be reported as exploratory.

The total number of patients accrued to this trial will be 18 to 36 patients. We anticipate accruing these patients within 2 years.

5.5 Data Safety and Monitoring Plan

5.5.1 Plan for monitoring the progress of the trial and the safety of participants

- PI will assume primary responsibility for monitoring the progress of the trial and the safety of participants.
- As part of the NCI CCR, this trial may be selected at random to be monitored by the staff of Harris Technical, Inc.
- Data will also be submitted to the NCI IRB annually for continuing review and at the completion of the study.
- In addition, at monthly research/ protocol meetings, senior staff of the NCI ROB will review protocol progress and provide feedback to the PI.

5.5.2 Plan for assuring the compliance with the requirements for reporting adverse events

- Adverse events will be reported as in section 5.3 and 7.3

5.5.3 Plan for assuring that any action resulting in suspension of the trial is reported to the IRB

This is an intramural NCI CCR protocol without external sponsors. If the NCI IRB issued the suspension, it would necessarily be aware. If another group issued a suspension of the trial, the PI would assume responsibility for notifying the NCI IRB.

5.5.4 Plan for assuring data accuracy and protocol compliance

- Data will be collected as in section 5.1
- Clinical data will be recorded in either the 4th Dimension Database or in the NCI CCR database or both.
- Data integrity and protocol adherence are assured by regular data verification and protocol compliance checks performed by the research team (PI, research nurse, data manager and clinic nurse).

6.0 HUMAN SUBJECTS PROTECTIONS

6.1 RATIONALE FOR SUBJECT SELECTION

This is a study for patients with prostate cancer. The patient population in whom this disease occurs is older adult males. This disease does not occur in children; therefore, children will not be part of this study. All ethnic groups/ race categories would be represented as they are represented in the disease as a whole. Decisionally impaired individuals

will not be included in this study, if they are unable to sign informed consent. Physically impaired persons who otherwise satisfy eligibility criteria will be included in this study.

6.2 PARTICIPATION OF CHILDREN

Adenocarcinoma of the prostate is not a disease of children, therefore, children will not be considered as research subjects for this study.

6.3 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

The medical risks associated with this study are those normally expected risks associated with external beam radiotherapy for prostate cancer. Common acute and temporary side effects include fatigue, urethritis, cystitis and proctitis. Uncommon long-term side effects may include urinary frequency, urgency, incontinence, rectal bleeding, perineal pain, tenesmus, erectile dysfunction, and infertility. Very rare long-term complications may include lymphedema, pathologic femoral neck fractures, and a second primary malignancy.

Patients on this study will be receiving treatment for their prostate cancer. Other potential benefits of participation may include fewer side effects of radiation treatment due to a better visualization of the anatomy and sparing of normal structures. The information learned from this study may also benefit other patients with prostate cancer in the future.

6.4 CONSENT AND ASSENT PROCESSES AND DOCUMENTS

The Principal Investigator and associates will recruit patients. The investigational nature and objectives of this study, the procedures involved and their attendant risks and discomforts, will be carefully explained to the patient, and a signed informed consent document will be obtained. It is our goal to be as explicit as possible in verbal and written consent procedures to insure that all participants are joining the study without coercion.

Patients who meet study eligibility criteria, and who are willing to participate in the study, will be consented by the PI or associate investigators. The consent form will be discussed with the patient in person. Informed consent will involve careful explanation of all items outlined in the consent form. This discussion includes the investigational nature of this study, and the possibility of lack of direct benefit to the research subject. All information will be reported in summary fashion only. A separate anesthetic/operative consent will be obtained at the time of the procedure

6.5 PATIENT ADVOCATE

The patient's rights representative is available to patients on this protocol at (301) 496-2626 in Building 10, Room 1C132, NIH. Patients may ask any questions about the study and may withdraw their consent at any time without compromising their medical care.

7.0 DATA REPORTING

7.1 PATIENT REGISTRATION FORM

Demographic information and results of pretreatment studies should be entered and reported to Harris Technical, Inc., at the time of patient entry onto the trial (see section 2.3).

7.2 DATA SUBMISSION

- Summary information will be submitted to the IRB annually for continuing review and at the completion of the study.
- Data may be reported in laboratory publications as derived from pilot studies. Patients will not be indicated by name.
- The number of MR-identified abnormalities in the initial evaluation that are biopsied and whether or not they are confirmed pathologically as cancer will be reported in the annual continuing review application to NCI IRB.

7.3 Definitions

7.3.1 Adverse Events

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form unless otherwise noted above in Section 5.1.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution. AEs should be reported up to 30 days following the last dose of study drug.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms

- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

7.3.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

7.3.3.Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.3.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

7.3.5 Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.3.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

7.3.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

7.3.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB-approved research protocol.

7.3.9 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

7.3.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to
 - (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and
 - (b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a *greater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.4 NCI-IRB REPORTING

7.4.1 NCI-IRB Expedited Reporting of Unanticipated Problems and Deaths

The NCI-IRB **requires** that the following language be used for reporting events to the NCI-IRB:

The Protocol PI will report to the NCI-IRB:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All serious non-compliance

Reports must be received by the NCI-IRB within 7 working days of PI awareness via iRIS.

7.4.2 NCI-IRB Requirements for PI Reporting at Continuing Review

*For reporting of adverse events at time of continuing review, the NCI-IRB requires a summary report of adverse events that have occurred on the protocol **since the previous continuing review and in aggregate**. The method of presentation should provide the NCI-IRB with the information necessary to clearly identify risks to participants and to make a risk: benefit determination. Please sort the events by the system organ class and by grade. The summary report is based on the following guidance: any unexpected severity and/or unexpected frequency of expected events needs to be reported and interpreted in relation to the risk: benefit of study participants in the narrative.*

Please use following table for reporting adverse events at time of CR:

System Organ Class	CTCAE Term	Grade	# of Events since last CR	Total # of Events	Attribution to Research	Serious?	Unexpected?

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:

- All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
- All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
- All Grade 5 events regardless of attribution;
- All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

8.0 PHARMACEUTICAL INFORMATION

8.1. Levofloxacin:

Manufacturer: Ortho-McNeil

Commercial Name: Levaquin®

Description: Levofloxacin is a synthetic broad spectrum antibacterial agent in the family of fluoroquinolones for oral administration.

Form: Levofloxacin is available as (-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyridol[1,2,3-del]-1,4-benzoxazine-6-carboxylic acid hemihydrate. It is available in 250, 500 and 750 mg film-coated tablets. The inactive ingredients are starch, microcrystalline cellulose, crospovidone, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, polysorbate 80 and synthetic red and yellow iron oxides.

Supply: Levofloxacin is commercially available and will be supplied by the Clinical Center pharmacy.

Toxicities: Nausea, diarrhea, vomiting, and abdominal pain are the most frequent side effects of levofloxacin. Bad taste in the mouth, restlessness, rash, sensitivity to sunlight and seizures are other possible side effects. Levaquin may cause dizziness or lightheadedness.\

Levofloxacin should be administered at least 2 hours before or 6 hours after magnesium/aluminum antacids, or sucralfate, Videx® (didanosine) chewable/buffered tablets or pediatric powder for oral solution, or other products containing calcium, iron or zinc.

8.2 Bupivacaine:

Manufacturer: Abbott Pharmaceutical

Commercial Name: Marcaine®

Description: Bupivacaine is a long-acting local anesthetic administered by parenteral injection. It is a homologue of mepivacaine and is chemically related to lidocaine in the class of depolarizing local anesthetics.

Form: Bupivacaine is available as 2-piperidinecarboxamide, 1-butyl-N-(2,6-dimethylphenyl)-, monohydrochloride, monohydrate. It is available as a sterile injectable liquid in 0.25, 0.5, and 0.75% concentrations packaged in single use ampules ranging from 10 to 50 ml. The inactive ingredients are sodium chloride and hydrochloric acid.

Supply: Bupivacaine is commercially available and will be supplied by the Clinical Center pharmacy.

Toxicities: Adverse reactions and systemic toxicities are predominantly related to the dosage and of route injection. Maximal dosage is 150 mg in adult patients. A 10 ml dose of 0.25% contains 25 mg of bupivacaine. Central nervous system toxicities include restlessness, anxiety, dizziness, tinnitus, blurred vision and tremors. Convulsions and seizures can result from excessive plasma levels. Cardiovascular toxicities from high doses or unintentional intravascular injection may lead to high plasma levels and related depression of the myocardium, decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation, and cardiac arrest. The use of low dosages of bupivacaine for regional blockade in peripheral sites not including the head and neck or obstetrical applications has a less than 0.01% chance of adverse reaction. Severe cardiac or neurologic toxicity with its use in prostate biopsy has not been reported.

8.3 MRI CONTRAST AGENT – Gadopentate dimeglumine Manufacturer: Berlex Laboratories, Wayne NJ

Commercial name: Magnevist

Description: This is an FDA approved contrast agent in widespread use. Gadolinium produces MR contrast by altering the relaxivity of neighboring water protons. Experience at NIH has been obtained with over 30,000 intravenous injections.

Form: Gadopentate dimeglumine is available as Gd-DTPA. It is available as a sterile injectable liquid in single use ampules of 20 ml. The inactive ingredients are meglumine and diethylenetriamine pentaacetic acid.

Supply: Magnevist is commercially available and will be supplied by the Clinical Center Department of Radiology

Toxicities: The serious reaction rate (asthma, hives, seizures, hypotension) is less than 0.5%. The dose is 0.1 mmol/kg BW administered IV bolus via mechanical injector. There are no contraindications for its use. Gd-DTPA can be used in patients with elevated Cr. Levels and does not have known nephrotoxicity. Possible complications relate to extravasation of contrast in which localized swelling and pain may develop but because of the small volume (20cc) this does not lead to skin necrosis. There may be headache, nausea, vomiting, and transient sensations of heat or cold or taste disturbances following injection of gadopentetate.

8.4 Fleet Phospho-soda® enema

Manufacturer: C.B. Fleet Co. Inc., Lynchburg, VA

Description: A sodium phosphate solution for cleansing of the rectal mucosa prior to invasive procedures.

Form: Each 118 ml delivered dose includes 19g of monobasic sodium phosphate and 7 g of dibasic sodium phosphate. Latex-free application bottles contain 133 ml of solution.

Supply: Fleet® enema is commercially available and will be supplied by the Clinical Center pharmacy.

Toxicities: Fleet® enema cannot be used in patients with congenital megacolon, bowel obstruction, imperforate anus, or congestive heart failure. It must be used with caution in patient with impaired renal function, pre-existing electrolyte disturbances or a colostomy, or in patients on diuretics or other medications that may affect electrolyte levels. Hypocalcemia, hyperphosphatemia, hypernatremia, or acidosis may occur.

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AUA SYMPTOM SCORE

Last Name	First Name	Date

Highlight or bold or change font color of the response correct for you and type in your score in the far right box for all SEVEN questions.

1. **Incomplete emptying:** Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?

Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your Score
0	1	2	3	4	5	

2. **Frequency:** Over the past month, how often have you had to urinate again less than 2 hours after you finished urinating?

Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your Score
0	1	2	3	4	5	

3. **Intermittency:** Over the past month, how often have you found that you stopped and started again several times when you urinated?

Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your Score
0	1	2	3	4	5	

4. **Urgency:** Over the past month, how often have you found it difficult to postpone urination?

Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your Score
0	1	2	3	4	5	

5. **Weak-stream:** Over the past month, how often have you had a weak stream?

Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your Score
0	1	2	3	4	5	

6. **Straining:** Over the past month, how often have you had to push or strain to begin urination?

Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	Your Score
0	1	2	3	4	5	

7. **Nocturia:** Over the past month or so, how many times did you get up to urinate from the time you went to bed until the time you got up in the morning?

None	1 time	2 times	3 times	4 times	5 or more times	Your Score
0	1	2	3	4	5	

Add up your scores for total AUA score = _____

Quality of Life Due to Urinary Symptoms: If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that? (Bold, Highlight or Underline)

Delighted Pleased Mostly satisfied Mixed Mostly dissatisfied Unhappy Terrible

Physician Signature _____ Date _____

SEXUAL HEALTH INVENTORY FOR MEN (SHIM)

PATIENT NAME: _____

TODAY'S DATE: _____

PATIENT INSTRUCTIONS

Sexual health is an important part of an individual's overall physical and emotional well-being. Erectile dysfunction, also known as impotence, is one type of very common medical condition affecting sexual health. Fortunately, there are many different treatment options for erectile dysfunction. This questionnaire is designed to help you and your doctor identify if you may be experiencing erectile dysfunction. If you are, you may choose to discuss treatment options with your doctor.

Each question has several possible responses. Circle the number of the response that **best describes** your own situation. Please be sure that you select one and only one response for **each question**.

OVER THE PAST 6 MONTHS:

1. How do you rate your confidence that you could get and keep an erection?		VERY LOW	LOW	MODERATE	HIGH	VERY HIGH
		1	2	3	4	5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?	NO SEXUAL ACTIVITY	ALMOST NEVER OR NEVER	A FEW TIMES (MUCH LESS THAN HALF THE TIME)	SOMETIMES (ABOUT HALF THE TIME)	MOST TIMES (MUCH MORE THAN, HALF THE TIME)	ALMOST ALWAYS OR ALWAYS
	0	1	2	3	4	5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	DID NOT ATTEMPT INTERCOURSE	ALMOST NEVER OR NEVER	A FEW TIMES (MUCH LESS THAN HALF THE TIME)	SOMETIMES (ABOUT HALF THE TIME)	MOST TIMES (MUCH MORE THAN, HALF THE TIME)	ALMOST ALWAYS OR ALWAYS
	0	1	2	3	4	5
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	DID NOT ATTEMPT INTERCOURSE	EXTREMELY DIFFICULT	VERY DIFFICULT	DIFFICULT	SLIGHTLY DIFFICULT	NOT DIFFICULT
	0	1	2	3	4	5
5. When you attempted sexual intercourse, how often was it satisfactory for you?	DID NOT ATTEMPT INTERCOURSE	ALMOST NEVER OR NEVER	A FEW TIMES (MUCH LESS THAN HALF THE TIME)	SOMETIMES (ABOUT HALF THE TIME)	MOST TIMES (MUCH MORE THAN, HALF THE TIME)	ALMOST ALWAYS OR ALWAYS
	0	1	2	3	4	5

Add the numbers corresponding to questions 1-5.

TOTAL: _____

The Sexual Health Inventory for Men further classifies ED severity with the following breakpoints:

1-7 Severe ED

8-11 Moderate ED

12-16 Mild to Moderate ED

17-21 Mild ED

Physician Signature _____ Date _____

